A MULTICOMPONENT MEDICATION PROMOTES CHONDROGENESIS AND REDUCES MMP-13

in primary articular chondrocytes from knee OA patients in vitro

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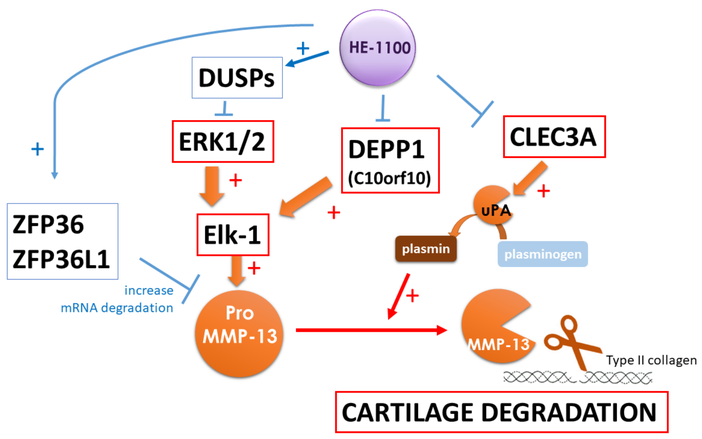
PURPOSE. HE-1100 is a multicomponent medicinal product. Initial preclinical data potentially suggest a preventive effect on cartilage degradation. This study aims to understand the mode of action of HE-1100 on OA chondrocytes in vitro.

METHODS. Primary chondrocytes were obtained from 10 knee osteoarthritis (OA) patients undergoing knee replacement surgery. The cultures were treated with 20% (v/v) HE-1100 or placebo. Samples were collected for subsequent RNA extraction using standard methods. The reads were generated with Illumina NextSeq5000 sequencer and aligned to the human reference genome (UCSC hg19) to generate the transcriptome. Differential expression analysis between HE-1100 and placebo was made in R using the DESeq2 package to identify the differentially expressed genes in the OA-associated regulatory pathways. The protein production of the selected genes was quantified by ELISA in 10 independent human OA chondrocytes cultures.

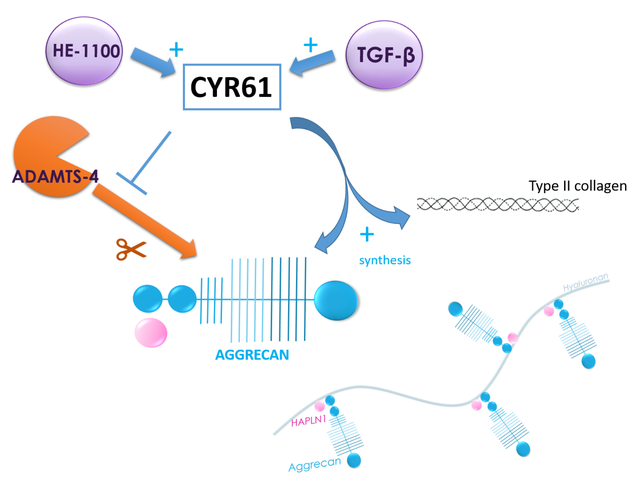
RESULTS

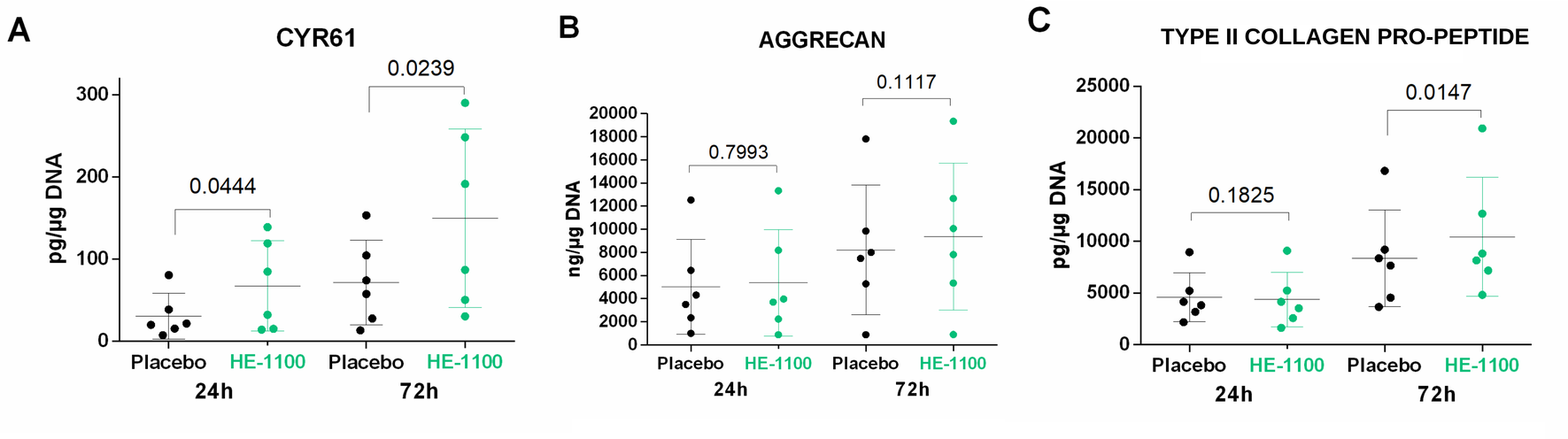
HE-1100 significantly modified the expression of 13 genes in OA chondrocytes by at least 10% with an adjusted p-value < 0.05 : **EGR1** (+93%), **FOS** (+87%), **NR4A1** (+43%), **DUSP1** (+18%), **ZFP36** (+18%), **ZFP36L1** (+14%), **NFKBIZ** (+16%) **and CYR61** (+14%) were upregulated and **ATF7IP** (-10%), **TXNIP** (-11%), **C10orf10** (-12%), **CLEC3A** (-12%) and **MMP13** (-18%) were downregulated after 24h HE-1100 treatment.

Activity of HE-1100 on MMP-13 pathway



Activity of HE-1100 on chondrogenesis through CYR61





A) HE-1100 significantly increased the **CYR61 protein** production in human OA chondrocytes (2.3 fold +/- 1.2 after 24h and 2.3 fold +/- 1.0 after 72h). **B)** and **C)** After 72h, HE-1100 increased, but not significantly, **aggrecan production** by 14 ± 19 % and significantly increased **type II collagen pro-peptide production** by 27 ± 20 %. For both time points CYR61 production by OA chondrocytes was positively and significantly correlated with aggrecan (r=0.66, p=0.0004) and type II collagen pro-peptide (r=0.64, p=0.0008) production. **D)** In alginate beads culture, **pro-MMP-13** was significantly decreased in HE-1100 treated cultures from day 7 to day 14 (from -16 to -25 %, p<0.05) and from day 17 to 21 (-22 %, p=0.0331) in comparison to controls.

CONCLUSION

HE-1100 significantly modified the expression of DUSP1, C10orf10, ZFP36/L1 and CLEC3A, which are pathway mediators involved in MMP-13 expression and activation. Further, long-term (28 days) treatment with HE-1100 significantly reduced the production of pro-MMP-13, the inactive precursor of the metalloproteinase MMP-13 involved in type II collagen degradation. HE-1100 also promoted extracellular matrix formation probably through CYR61 production, a growth factor well correlated with type II collagen and aggrecan production.

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